OLUX-E - clobetasol propionate aerosol, foam
Stiefel Laboratories

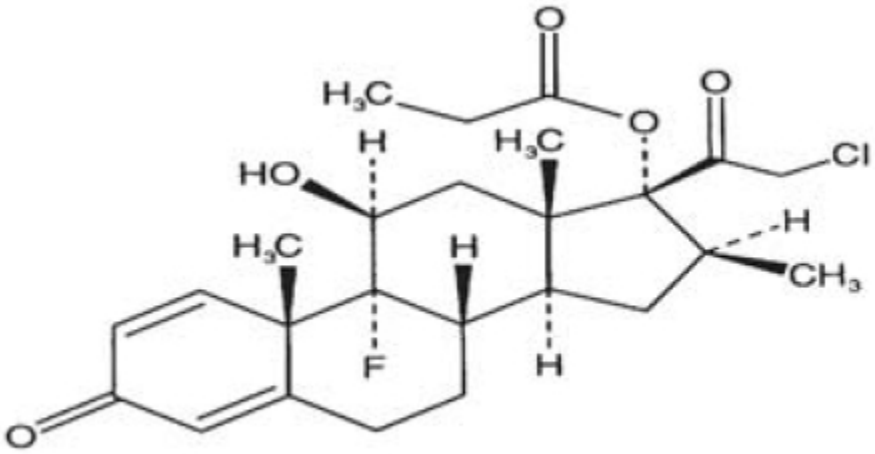
Rx Only
FOR TOPICAL USE ONLY
NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE

DESCRIPTION

Olux-E (clobetasol propionate) Foam, an emulsion aerosol foam, contains the active ingredient clobetasol propionate, USP, a synthetic corticosteroid for topical dermatologic use. Clobetasol, an analog of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity.

Clobetasol propionate is 21-chloro-9-fluoro-11ß,17-dihydroxy-16ß-methylpregna1,4-diene-3,20-dione 17-propionate, with the empirical formula $C_{25}H_{32}ClFO_5$, and a molecular weight of 466.97. The following is the chemical structure:

Figure 1: Structural Formula



Clobetasol Propionate, USP

Clobetasol propionate is a white to cream-colored crystalline powder, practically insoluble in water.

Each gram of Olux-E Foam contains 0.5 mg clobetasol propionate, USP. The foam also contains anhydrous citric acid USP, cetyl alcohol NF, cyclomethicone NF, isopropyl myristate NF, light mineral oil NF, polyoxyl 20 cetostearyl ether NF, potassium citrate monohydrate USP, propylene glycol USP, purified water USP, sorbitan monolaurate NF, white petrolatum USP, and phenoxyethanol NF as a preservative.

Olux-E Foam is dispensed from an aluminum can pressurized with a hydrocarbon (propane/butane) propellant.

CLINICAL PHARMACOLOGY

The contribution to efficacy by individual components of the vehicle has not been established.

Topical corticosteroids share anti-inflammatory, antipruritic, and vasoconstrictive properties.

The mechanism of the anti-inflammatory activity of topical steroids is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

Pharmacokinetics

Topical corticosteroids can be absorbed from intact healthy skin. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the product formulation and the integrity of the epidermal barrier. Occlusion, inflammation and/or other disease processes in the skin may increase percutaneous absorption. The use of pharmacodynamic endpoints for assessing the systemic exposure of topical corticosteroids may be necessary due to the fact that circulating levels are often below the level of detection. Once absorbed through the skin, topical corticosteroids are metabolized, primarily in the liver, and are then excreted by the kidneys. Some corticosteroids and their metabolites are also excreted in the bile.

Following twice daily application of Olux-E Foam for one week to 32 adult patients with mild to moderate plaque-type psoriasis, mean peak plasma concentrations (±SD) of 59 ± 36 pg/mL of clobetasol were observed at around 5 hours post-dose on day 8.

CLINICAL STUDIES

In a randomized study of subjects 12 years of age and older with moderate to severe atopic dermatitis, 251 subjects were treated with Olux-E Foam and 126 subjects were treated with Vehicle Foam. Subjects were treated twice daily for two weeks. At the end of treatment, 131 of 251 subjects (52%) treated with OluxE Foam compared with 18 of 126 (14%) treated with Vehicle Foam achieved

treatment success. Treatment success was defined by an Investigator's Static Global Assessment (ISGA) score of clear (0) or almost clear (1) with at least 2 grades improvement from baseline, and scores of absent or minimal (0 or 1) for erythema and induration/ papulation.
In an additional randomized study of subjects 12 years of age and older with mild to moderate plaque-type psoriasis, 253 subjects were treated with Olux-E Foam and 123 subjects were treated with Vehicle Foam. Subjects were treated twice daily for two weeks. At the end of treatment, 41 of 253 subjects (16%) treated with Olux-E Foam compared with 5 of 123 (4%) treated with Vehicle Foam achieved treatment success. Treatment success was defined by an Investigator's Static Global Assessment (ISGA) score of clear (0) or almost clear (1) with at least 2 grades improvement from baseline, scores of none or faint/minimal (0 or 1) for erythema and scaling, and a score of none (0) for plaque thickness.

INDICATIONS AND USAGE

Olux-E Foam is indicated for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 12 years of age or older (see PRECAUTIONS). Treatment should be limited to 2 consecutive weeks and patients should not use greater than 50 grams per week (see DOSAGE AND ADMINISTRATION).
Patients should be instructed to use Olux-E Foam for the minimum amount of time necessary to achieve the desired results (see PRECAUTIONS).
Use in pediatric patients under 12 years of age is not recommended because of numerically high rates of hypothalamic-pituitary-adrenal (HPA) axis suppression seen in patients under 12 years of age (see PRECAUTIONS: Pediatric Use).

CONTRAINDICATIONS

Olux-E Foam is contraindicated in patients who are hypersensitive to clobetasol propionate or to any ingredient in this preparation.

WARNINGS

The propellant in Olux-E Foam is flammable. Avoid fire, flame or smoking during and immediately following application.

PRECAUTIONS

General

Olux-E Foam has been shown to suppress the HPA axis.
Systemic absorption of topical corticosteroids has caused reversible adrenal suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.
Pediatric patients may be more susceptible to systemic toxicity from equivalent doses because of their larger skin surface to body mass ratios (see PRECAUTIONS: Pediatric Use).
Conditions which increase systemic absorption include the application of more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Therefore, patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of adrenal suppression (see laboratory tests below). If adrenal suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur, requiring supplemental systemic corticosteroids.
In a study evaluating the potential for HPA axis suppression, using the cosyntropin stimulation test, Olux-E Foam demonstrated adrenal suppression after two weeks of twice daily use in patients with atopic dermatitis of at least 30% body surface area (BSA). The proportion of subjects twelve years of age and older demonstrating HPA axis suppression was 16.2% (6 out of 37). In this study HPA axis suppression was defined as serum cortisol level ≤18 mcg/dL 30-min post cosyntropin stimulation. The laboratory suppression was transient; in all subjects serum cortisol levels returned to normal when tested 4 weeks post treatment.
Patients with acute illness or injury may have increased morbidity and mortality with intermittent HPA axis suppression.
Patients should be instructed to use Olux-E Foam for the minimum amount of time necessary to achieve the desired results (see INDICATIONS AND USAGE).
If irritation develops, Olux-E Foam should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a *failure to heal* rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.
If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of Olux-E Foam should be discontinued until the infection has been adequately controlled.
Olux-E Foam should not be used in the treatment of rosacea or perioral dermatitis, and should not be used on the face or the groin, axillae, or other intertriginous areas.

Information for Patients

Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Unless directed by the prescriber, it should not be used on the face, or in skin-fold areas, such as the underarms or groin. Avoid contact with the eyes or other mucous membranes. Wash hands after use.

2. This medication should not be used for any disorder other than that for which it was prescribed.

3. The treated skin area should not be bandaged, wrapped, or otherwise covered so as to be occlusive unless directed by the physician.

4. Patients should report any signs of local or systemic adverse reactions to the physician.

5. Patients should inform their physicians that they are using Olux-E Foam if surgery is contemplated.

6. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.

7. Patients should not use more than 50 grams per week of Olux-E Foam, or an amount greater than 21 capfuls per week (see DOSAGE AND ADMINISTRATION).

Laboratory Tests
The cosyntropin ($ACTH_{1-24}$) stimulation test may be helpful in evaluating patients for HPA axis suppression.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.
Clobetasol propionate was non-mutagenic in four different test systems: the Ames test, the mouse lymphoma test, the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* B WP2 fluctuation test. In the *in vivo* mouse micronucleus test a positive finding was observed at 24 hours, but not at 48 hours, following oral administration at a dose of 2000 mg/kg.
Studies in the rat following subcutaneous administration of clobetasol propionate at dosage levels up to 0.05 mg/kg per day revealed that the females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose.

Pregnancy

Teratogenic effects

Pregnancy Category C
Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

Clobetasol propionate has not been tested for teratogenicity when applied topically; however, it is absorbed percutaneously, and when administered subcutaneously, it was a significant teratogen in both the rabbit and the mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent.

Teratogenicity studies in mice using the subcutaneous route resulted in fetotoxicity at the highest dose tested (1 mg/kg) and teratogenicity at all dose levels tested down to 0.03 mg/kg. These doses are approximately 1.4 and 0.04 times, respectively, the human topical dose of Olux-E Foam based on body surface area comparisons. Abnormalities seen included cleft palate and skeletal abnormalities.

In rabbits, clobetasol propionate was teratogenic at doses of 0.003 and 0.01 mg/kg. These doses are approximately 0.02 and 0.05 times, respectively, the human topical dose of Olux-E Foam based on body surface area comparisons. Abnormalities seen included cleft palate, cranioschisis, and other skeletal abnormalities.

There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. Olux-E Foam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Because many drugs are excreted in human milk, caution should be exercised when Olux-E Foam is administered to a nursing woman.

Pediatric Use
Use in pediatric patients under 12 years of age is not recommended.
After two weeks of twice daily treatment with Olux-E Foam, 7 of 15 patients (47%) aged 6 to 11 years of age demonstrated HPA axis suppression. The laboratory suppression was transient; in all subjects serum cortisol levels returned to normal when tested 4 weeks post treatment.
In 92 patients from 12 to 17 years of age, safety was similar to that observed in the adult population. Based on this data, no adjustment of dosage of Olux-E Foam in adolescent patients 12 to 17 years of age is warranted.
Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during and/or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.
HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema. Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

Geriatric Use
A limited number of patients at or above 65 years of age have been treated with Olux-E Foam (n = 58) in US clinical trials. While the number of patients is too small to permit separate analysis of efficacy and safety, the adverse reactions reported in this population were similar to those reported by younger patients. Based on available data, no adjustment of dosage of Olux-E Foam in geriatric patients is warranted.

ADVERSE REACTIONS
In controlled clinical trials involving 821 subjects exposed to Olux-E Foam and Vehicle Foam, the pooled incidence of local adverse reactions in trials for atopic dermatitis and psoriasis with Olux-E Foam was 1.9% for application site atrophy and 1.6% for application site reaction. Most local adverse events were rated as mild to moderate and they were not affected by age, race or gender. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
The following additional local adverse reactions have been reported with topical corticosteroids: folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, irritation, striae, and miliaria. They may occur more frequently with the use of occlusive dressings and higher potency corticosteroids, such as clobetasol propionate.
Cushing's syndrome has been reported in infants and adults as a result of prolonged use of topical clobetasol propionate formulations.

OVERDOSAGE
Topically applied Olux-E Foam can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION
Apply a thin layer of Olux-E Foam to the affected area(s) twice daily, morning and evening. For proper dispensing of foam, shake the can, hold it upside down, and depress the actuator. Dispense a small amount of foam (not more than a dollop the size of a golf ball) and gently massage the medication into the affected areas (excluding the face, groin, and axillae) until the foam is absorbed. Avoid contact with the eyes.
Treatment should be limited to 2 consecutive weeks and patients should not use greater than 50 grams per week or an amount greater than 21 capfuls per week.
Therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary. Unless directed by a physician, Olux-E Foam should not be used with occlusive dressings.

HOW SUPPLIED
Olux-E (clobetasol propionate) Foam, 0.05% is supplied in 100 gram (NDC 63032-101-00) and 50 gram (NDC 63032-101-50) aluminum cans.
Store at controlled room temperature 68–77°F (20–25°C).
FLAMMABLE. AVOID FIRE, FLAME OR SMOKING DURING AND IMMEDIATELY FOLLOWING APPLICATION.
Contents under pressure. Do not puncture or incinerate. Do not expose to heat or store at temperatures above 120°F (49°C).
Avoid contact with eyes or other mucous membranes.
Keep out of reach of children.
Manufactured for
Stiefel Laboratories, Inc.
Coral Gables, FL 33134
USA

For additional information:
1-888-500-DERM or visit
www.olux-e.com
U.S. Patent No. 6,730,288
U.S. Patent No. 7,029,659
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